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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 03/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/006,867	GODDARD ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-45,47 and 49-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42-45,47 and 49-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/9/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-41, 46 and 48 are cancelled.

Claims 42-44 and 52-53 have been amended.

2. Claims 42-45, 47 and 49-55 are pending and under examination.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. This office Action contains New Grounds of Rejections.

Rejections Withdrawn

5. The objections to the specification for containing embedded hyperlinks is withdrawn in view of the amendments to the specification filed 12/9/2005.

6. All rejections applied to claims 46 and 48 in the previous Office Action mailed 9/6/2005 are withdrawn in view of the cancellation of the claims.

7. The rejection of claims 42-44, 46-48, 50-55 under 35 U.S.C. 112, second paragraph as being indefinite as it pertains to the extracellular domain is withdrawn in view of the amendments to the claims.

8. The rejection of claims 42-44, 46, 48, 50-55 under 35 U.S.C. 112, second paragraph as being indefinite in the recitation "signal peptide" is withdrawn in view of the amendments to the claims.

9. The rejection of claims 42-44, 47-48 and 50-55 under 35 U.S.C. 112, first paragraph, NEW MATTER, as it pertains to the extracellular domain of SEQ ID NO:2 as being amino acids 34-366 is withdrawn in part in view of the amendments to the claims.

Response to Arguments

10. The rejection of claims 42-45, 47 and 49-55 under 35 U.S.C 101 because the claimed invention is not supported by a substantial asserted utility or a well-established utility is maintained.

The response filed 12/9/2005 has been carefully considered, but is deemed not to be persuasive. Applicant again reviews the evidentiary standard regarding the legal presumption of utility. The examiner takes no issue with Applicant's discussion of the evidentiary standard regarding the legal presumption of utility. Applicant argues again that the utility need not be proved to a statistical certainty, a reasonable correlation between the evidence and the asserted utility is sufficient and applicant cites numerous case law asserted to support applicants arguments that for a therapeutic and diagnostic use, utility does not have to be established to an absolute certainty and the evidence need not be direct evidence so long as there is a reasonable correlation between the evidence and the asserted utility. The examiner agrees with Applicant's statement that absolute certainty is not the legal standard for utility, however, the rejection does not question the presumption of truth, or credibility, of the asserted utility. The asserted utilities of cancer diagnostics and cancer therapeutics for the claimed polypeptides are credible and specific, however, they are not substantial. The data set forth in the specification are preliminary at best because the specification does not teach the expression of the PRO180 polypeptide nor any particular biological activity of the polypeptide. It remains that, there is no information on the record as to whether the claimed protein is expressed at all in lung and rectum tissue, cancerous or otherwise.

At pages 10-12 of the response Applicant summarizes their arguments and the disputed issues involved. Applicant reiterates that the data provided in Example 18 in the specification, which shows that mRNA encoding the PRO180 polypeptide is more highly expressed in normal lung and rectum tumor compared to lung tumor and normal rectum is sufficient to establish a specific and substantial utility for the claimed polypeptides.

Applicant argues Hu et al (2003, Journal of Proteome Research 2:405-412, of record) as being based upon a statistical analysis of information from published literature rather than from experimental data. Applicant characterizes Hu et al as being limited to estrogen-receptor-positive breast tumor only. Applicant criticizes the types of statistical tests performed by Hu. Applicant concludes that, based on the nature of the statistical analysis performed in Hu, and the fact that Hu only analyzed one class of genes, the conclusions drawn by the examiner are not reliably supported. This has been fully considered but is not found to be persuasive. The asserted utility for the claimed polypeptides is based on the presumption that increased mRNA production leads to increased protein production. Hu is directly on point by showing that this presumption is incorrect when designating protein as diagnostic markers for cancer. Hu analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant

correlation between expression level and a published role in the disease (see discussion section). One of the authors of this paper, Dr. LaBaer, made an even stronger statement that reports of mRNA or protein changes of as little as two-fold are not uncommon, and although changes of this magnitude may turn out to be important, most are attributable to disease-independent differences between the samples (emphasis added; 2003, Nature Biotechnology 21(9):976-977, Ids reference 10, filed 12/9/05). The instant specification does not disclose that PRO1069 mRNA levels are expressed at 10-fold or higher levels compared with normal, matched tissue samples. Therefore, based on Hu, the skilled artisan would not reasonably expect that PRO180 protein can be used as a cancer diagnostic. The instant specification does not provide additional information regarding whether or not PRO180 polypeptide is more highly expressed in normal lung and rectum tumor compared to lung tumor and normal rectum, and thus, the skilled artisan would need to perform additional experiments to reasonably confirm such. Since the asserted utility for the claimed polypeptides is not in currently available form, the asserted utility is not substantial. MPEP 2107 I states:

> A "substantial utility defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities.

In the instant case, the specification does not disclose further testing of PRO180 gene product expression levels. Therefore, the skilled artisan would have been required to do the testing. In view of such requirement, the products based on the claimed invention are not in "currently available" form, the asserted utility is not substantial.

Regarding Applicant's criticism of Hu et al's statistical analysis, Applicant is holding Hu et al to a higher standard than their own specification, which does not provide proper statistical analysis such as reproducibility, standard error rates, etc. Regarding Applicant's criticism of Hu et al as being limited to a specific type of breast tumor, Hu et al is cited as one of several pieces of evidence that gene expression in a tumor does not correlate protein expression. Considering the evidence of record as a whole, there is no reasonable correlation between mRNA levels and protein levels.

Applicants argue that the lack of a known role for PRO180 in cancer does not prevent its use as a diagnostic tool for cancer. Although, the utility is credible and specific it is not substantial. Applicant cites the PTO's written policies, which recognize that the utility of a nucleic acid does not depend on the function of the encoded gene product. The Utility Examination Guidelines published on January 5, 2001 state: "In addition, the utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have a specific and substantial utility because, e.g. it hybridises near a disease-associated gene or it has a gene regulating activity. " (Federal Register, Volume 66, page 1095, Comment 14). This has been fully considered but is not found persuasive. In the instant case, the instant claims are drawn to PRO180 polypeptide where the specification does not disclose a correlation between any specific disorder and an altered level or form of the claimed PRO180 polypeptide. Applicant states that the requirement for a known role for PRO180 in cancer for utility is inconsistent with the analogous standard for therapeutic utility of a compound where the mere identification of a pharmacological activity of a compound

that is relevant to an asserted pharmacological use provides an immediate benefit to the public and thus satisfies the utility requirement, citing M.P.E.P. § 2107 regarding the requirement for a substantial asserted utility. Applicant asserts that the mere identification of altered expression in tumors is relevant to diagnosis of tumors, and, therefore, provides an immediate benefit to the public. This has been fully considered but is not found to be persuasive. Unlike a compound where a pharmacological activity has been identified, an altered level or form of the claimed polypeptides has not been correlated with lung and rectum tissue, cancerous or otherwise and no activity has been identified for the claimed polypeptides. In the instant case, the asserted utility that PRO180 polypeptides are useful as diagnostic markers for cancer is not substantial in that further research is required to reasonably confirm a real world context of use. In order for PRO180 polypeptide to be useful as a cancer diagnostic, there must be a detectable change in the amount or form of the PRO180 polypeptide between cancerous and healthy tissue. In the instant case, the evidence of record indicates that (1) cDNA is "more highly expressed" in normal lung and rectum tumor compared to lung tumor and normal rectum (2) increased mRNA levels do not reliably correlate with increased polypeptide levels (Haynes et al, Gygi et al, Chen et al, Hanash S and Hanash et al). In view of this, the skilled artisan would have viewed the cDNA amplification results as preliminary with respect to the utility of the encoded polypeptides or the antibodies binding the polypeptide, and would have had to experiment further to reasonably confirm whether or not PRO180 polypeptides can be used as a cancer diagnostic agent.

Applicants contend that the data in Example 18 and the first Grimaldi declaration demonstrate that the mRNA encoding PRO180 is differentially expressed in rectal and lung tumors and is thus sufficient to establish the asserted utility. Further Appellants contend that Mr. Grimaldi is an expert in the field who conducted or supervised the experiments at issue and his declaration is based on personal knowledge of the relevant facts at issue. This has been fully considered but is not found to be persuasive. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). (1) In the instant case, the nature of the fact sought to be established is whether or not cDNA amplification is predictive of increased protein levels. (2) It is important to note that the instant specification only discloses cDNA amplification data for PRO180 (i.e., data regarding amplification of PRO180 mRNA), and does not disclose any information regarding PRO180 polypeptide levels. Furthermore, there is strong opposing evidence showing that mRNA amplification is not predictive of protein levels in normal and cancerous tissues and, in turn, that increased mRNA levels are frequently not predictive of increased polypeptide levels. See, e.g., Haynes et al., discussed below. (3) Regarding the interest of the expert in the outcome of the case, it is noted

that Mr. Grimaldi is named as one of the inventor and is employed by the assignee. (4) Finally, Mr. Grimaldi refers to facts; however, the data is not included in the declaration so the examiner could not independently evaluate them. In conclusion, the Examiner submits that based on consideration of the evidence as a whole, the rejection is proper.

Applicant asserts that it is well-established in the art that a change in the level of mRNA for a particular protein, generally leads to a corresponding change in the level of the encoded protein and based on the differential expression of the mRNA encoding the PRO180 polypeptide in lung and rectal tumor, it is likely that the PRO180 polypeptide is differentially expressed, which renders the PRO180 polypeptide useful as a diagnostic tool for the determination of the presence or absence of tumor.

Contrary to Applicants assertion that Haynes et al (Electrophoresis, 19:1862-1871, 1998, Ids reference 20 filed 5/31/05) does not contradict the utility and enablement of the instant claims, Haynes et al states that "These results suggest that even for a population of genes predicted to be relatively homogeneous with respect to protein half-life and gene expression, the protein levels cannot be accurately predicted from the level of the corresponding mRNA" (page 1863, 2nd paragraph). Applicants contend that Haynes et al did not examine whether a change in transcript level for a particular gene led to a change in the level of expression of the corresponding protein. Haynes et al had studied more than 80 polypeptides relatively homogeneous in half-life and expression level found no strong correlation between polypeptide (steady state) and transcript levels. Applicants assert that Haynes et al reported that they "found a general trend but no strong correlation between protein and transcript levels". However,

Applicants assert that inspection of Figure 1 shows clear correlation between the mRNA levels and protein levels measured. Further it is claimed that this correlation is confirmed by an inspection of the full-length research paper from which the data in Figure 1 were derived, (Gygi et al, Molecular and Cellular Biology, 1999, 1720-1730, Ids reference 19 filed 5/31/05). Although Applicants assert that there is a strong correlation between mRNA expression and protein expression, Gygi et al conclude that transcript levels provide little predictive value with respect to the extent of protein expression (page 1730, last line). Furthermore, Gygi et al clearly state that the correlation between mRNA and protein levels was insufficient to predict protein expression levels from quantitative mRNA data (see abstract). Applicants contend that Haynes and Gygi et al looked at the static level of mRNA across many genes, not changes in the level of expression for single gene. Thus, Applicant contends that Haynes and Gygi have nothing to do with changes in protein levels resultant from changes in mRNA levels because they did not examine whether a change in transcript level for a particular gene led to a change in the level of expression of the corresponding protein. Applicants appear to be holding Haynes and Gygi to a higher standard than their own specification, which does not provide any information or testing on whether a change in amount or form of the PRO180 polypeptide correlates with a change in PRO180 mRNA in normal lung and rectal tumors compared to lung tumors and normal rectum.

Appellants have not established that there exists a correlation between the mRNA levels and the protein levels of PRO180 either in steady state or in a dynamic changing environment (i.e., tumors). Appellants appear to argue that Haynes teaches

that there was a general trend but no strong correlation, between protein and transcript levels and there is a positive correlation between mRNA and protein among most of the 80 yeast proteins studied. On the another hand, Appellant argues that the Haynes et al did not compare mRNA expression levels and protein levels in the same yeast cells and thus the analysis by Haynes et al is not applicable to the present application.

Appellant's arguments have been fully considered, but are not found persuasive for the following reasons. First, Appellant ignores the overall teachings of Haynes et al. At the 2nd paragraph of the left column of page 1863, Haynes et al clearly states, "For some genes studied equivalent mRNA transcript level translated into protein abundances which varied by more than 50-fold. Similarly, equivalent steady state protein expression levels were maintained by transcript levels varying by as much as 40-fold". Haynes et al concluded that the polypeptide levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, 2nd paragraph, last two lines). Specifically, Haynes et al state, "These results suggest that even for a population of genes predicted to be relatively homogenous with respect to protein half-life and gene expression, the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript" (p. 1863, 2nd paragraph, last five lines). Haynes et al also state, "only the direct analysis of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts" (p. 1870, under concluding remarks). Accordingly, the limited disclosure in the instant case does not meet the legal standard for a substantial utility and the examiner declines to attenuate the standard to the extent of applicant.

At the middle of pages 19-21 of the response, Applicants assert that Chen et al. (2002, Molecular and Cellular Proteomics 1:304-313, cited on PTO-892 mailed 4/9/04) is not relevant to Applicant's assertion that changes in the level of mRNA lead to changes in the level of the encoded polypeptide. Applicant's argue that Chen et al read in its entirety provides scant evidence to counter Appellants' asserted utility because portions of reference support Applicants assertions, and the remaining portions provide little insight into the relationship between changes in mRNA levels and changes in the corresponding protein levels for mRNA that is differentially expressed in tumor cells relative to normal cells. Applicants argument has been fully considered, but is not deemed to be persuasive for the following reasons. Chen et al compared mRNA and protein expression levels within the same tumor samples and found only 17% of 165 protein spots or 21% (21of 98 genes) show a statistically significant correlation between mRNA and protein. Chen et al clearly state that "[T]he use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products, as additional post-transcriptional mechanisms, including protein translation, post-translational modification, and degradation, may influence the level of protein present in a given cell or tissue" (p. 304, 2nd column) and "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples" (pp. 311-312). Chen et al summarize their findings by stating, using a quantitative analysis of mRNA and protein expression within the same lung adenocarcinomas, we showed that only a subset of the proteins exhibited a significant correlation with mRNA abundances" (abstract). Applicant refers to the citation of Celis

et al (FEBS Letters 480:2-16, 2000), in Chen et al, however, the Celis article has not been supplied for consideration and the specifics of the study of Celis are not clear. Furthermore, as with the Haynes et al reference above, Appellants are challenging portions of the reference selectively, including the assertion that the reference does not address the change in the mRNA levels and changes in protein levels, Applicants are again arguing limitations that are not recited in the claims and are ignoring the overall conclusions of the authors, which clearly state that correlations between mRNA and protein are lacking. The Chen reference taken as a whole clearly argues against Applicants position that there is, in general, a correlation between mRNA and protein expression. Since, the instant specification does not provide additional information regarding whether or not PR0180 polypeptide is more highly expressed in normal lung and rectal tumors compared to lung tumors and normal rectum, and thus the skilled artisan would need to perform additional experiments to reasonably confirm such. Therefore, the asserted utility for the claimed polypeptides is not in currently available form, the asserted utility is not substantial.

In agreement with the findings and conclusions of Haynes et al, Gygi et al and Chen et al, Hanash S. (Nature Reviews, Applied Proteomics Collection, pp.9-14, March 2005, Ids reference 2 filed 7/1/05) states "There is a need to profile gene expression at the level of the proteome and to correlate changes in gene-expression profiles with changes in proteomic profiles. The two are not always linked-numerous alterations occur in protein levels that are not reflected at the RNA level." (see page 12). Further, Hanash S. indicates that tumors are complex biological systems and no single type of

molecular approach fully elucidates tumor behavior, necessitating analysis at multiple levels encompassing genomics and proteomics (see abstract). Additionally, Hanash et al (The Pharmacogenomics Journal, 3(6):308-311, 2003, Ids reference 1 filed 7/1/05) states "However perfected DNA microarrays and their analytical tools become for disease profiling, they will not eliminate a pressing need for other types of profiling technologies that go beyond measuring RNA levels, particularly for disease-related investigations." (see page 311). Further, Winstead states "For all the information gene microarrays provide, they reveal relatively little about proteins, the molecules that carry out most of the functions of a cell. Gene arrays detect the presence of messenger RNA, the chemical involved in translating DNA into protein. Tracking this middle step in the production process reveals nothing about three areas of interest to researchers: protein function, the abundance of protein in a cell, and modifications to proteins after they are produced – changes that may be critical in the development of disease." (top of pg. 3) (Winstead E. R., Genome News Network, "The Evolving Art of Arrays", www.genomenewsnetwork.org, pp. 1-4, 15 September 2000). Irving et al (Nature Biotechnology 18:932-933, September 2000) state: "But despite their obvious value in gene expression profiling, such arrays reveal relatively little information about the final concentrations of gene products in a cell, and they reveal nothing about post-translational modifications, protein activity, and protein-protein interactions (pg. 932, top left column). In view of the totality of evidence, the skilled artisan would not reasonably presume that PRO180 polypeptide is more highly expressed in normal lung and rectum tumors compared to lung tumors and normal rectum based on the disclosure regarding

"more highly expressed" PRO180 mRNA without actually testing for PRO180 polypeptide expression. The requirement for such testing indicates that the asserted utility is not substantial, i.e., it requires further research to identify or confirm a "real world" use. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. This situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sup. Ct, 1966), in which the court held that

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field" and "a patent is not a hunting license" "[i]t is not a reward for the search, but compensation for its successful conclusion.".

Appellants contend on page 22 of the response, that it is well established in the art that in most cases a change in the level of mRNA for a particular protein leads to corresponding change in the level of the encoded protein. Appellants assert that the second Declaration provided by Mr. Grimaldi supports this assertion. Citing paragraph 5, of the declaration Appellants contend that 'those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed... the gene product or polypeptide will also be over-expressed... This same principle also applies to gene under-expression." At paragraph 4 of the second Grimaldi Declaration, the Declarant discusses mutations of Her2/Neu (c-erbB2), and chromosomal translocations that are

known to be associated with cancer, and states that "If the chromosomal aberration results in the aberrant expression of a mRNA and the corresponding gene product (the polypeptide) as they do in the aforementioned cases, then the gene product is a promising target for cancer therapy, for example, by the therapeutic antibody approach." This argument has been fully considered but is not deemed persuasive because it evinces that the instant specification provides a mere invitation to experiment, and not a readily available utility. The PRO180 gene, unlike Her2/Neu, has *not* been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. Similarly, unlike t (5;14), no translocation of PRO180 gene is known to occur. All that the specification demonstrates is that the PRO180 mRNA acid was more highly expressed in melanoma compared to normal skin tissue. No mutation or translocation of PRO180 has been associated with melanomas. In the absence of any of the above information, all that the specification does is present evidence that the cDNA encoding PRO180 polypeptide is amplified in an unknown number of samples, and invite the artisan to determine the rest of the story. Such is insufficient to meet the requirements of 35 U.S.C. § 101 for the claimed antibodies binding the polypeptides.

In addition, beginning at page 22 of the response, Applicant points to the declaration of Dr. Polakis, submitted under 37 C.F.R. 1.132 with the response filed 07 July 2004. Appellant characterizes the declaration as setting forth Dr. Polakis experience with microarray analysis wherein approximately 200 gene transcripts present in human tumor cells were found to be at significantly higher levels than in corresponding normal human cells. The declaration goes on to state that antibodies

binding to about 30 of these tumor antigens were prepared, and mRNA and protein levels compared. The declaration states that in approximately 80% of the cases, the researchers found that increased levels of RNA correlated with changes in the level of protein. Applicant concludes that all of the submitted evidence supports Applicant's position that it is more likely than not that increased gene amplification levels predict increased mRNA and increased protein levels, thus meeting the utility standards. This has been fully considered but is not found to be persuasive. In assessing the weight to be given to expert testimony, the examiner may properly consider, among other things, (1) the nature of the fact sought to be established, (2) the strength of any opposing evidence, (3) the interest of the expert in the outcome of the case, and (4) the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). (1) In the instant case, the nature of the fact sought to be established is whether or not gene amplification is predictive of increased mRNA levels and, in turn, increased protein levels. Dr. Polakis declares that 80% of approximately 200 instances of elevated mRNA levels were found to correlate with increased protein levels. (2) It is important to note that the instant specification only discloses mRNA expression data for PRO180, and does not disclose any information regarding PRO180 protein levels. Furthermore, there is strong opposing evidence showing that increased mRNA levels are frequently not predictive of increased polypeptide levels. See, e.g., Chen et al (who found only 17% of 165 polypeptide spots

or 21% of the genes had a significant correlation between polypeptide and mRNA expression levels in lung adenocarcinoma samples), Hu et al, LaBaer, Haynes et al, Gygi et al, Hanash S., Hanash et al, Winstead E. R. and Irving et al, (3) Regarding the interest of the expert in the outcome of the case, it is noted that Dr. Polakis is employed by the assignee. (4) Finally, Dr. Polakis refers to facts; however, the data is not included in the declaration so the examiner could not independently evaluate them.

Applicants, along with the Grimaldi and Polakis declarations, Applicants also provide teachings from Molecular Biology of the Cell by Bruce Alberts and Genes VI (1997) by Benjamin Lewin (filed 12/13/2004), to support their assertion that there is a correlation between increased gene expression and increased protein expression. Applicants also refer to additional articles by Zhigang et al (Ids filed 5/31/05), and Meric et al (Ids field 5/31/05) as providing evidence that gene amplification generally results in elevated levels of the encoded polypeptide. Zhigang et al describe a specific example of the expression of prostrate stem cell antigen (PSCA) protein and mRNA to validate it as potential molecular target for diagnosis and treatment of human prostate cancer. It is asserted that the data shows "a high degree of correlation between PSCA protein and mRNA expression". Further Meric et al states "the fundamental principle of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells. Meric et al also teaches that most efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. Although, Appellants contend that the regulation is primarily at the transcriptional level (based on

teachings found in Molecular Biology of the Cell), the prior art references evince that gene expression is quite complicated and is regulated at the level of mRNA transcription, mRNA stability, mRNA translation and protein stability (e.g., Meric et al at page 971, left column, first paragraph of introduction). In addition, unlike the instant invention, Zhigang et al provide immunohistochemical analysis and mRNA hybridization to correlate the mRNA expression with the protein for a known prostate stem cell antigen (PSCA). Unlike the instant PRO1864 polypeptide, PSCA is well characterized and is a cell surface antigen that is predominantly prostate specific (see page 2). Further, the focus of efforts to exploit differences in gene expression at the level of mRNA between cancer cells and normal cells coincided with the advent of cDNA array technology, which facilitated this type of approach (Meric et al, p. 971, left column first paragraph of introduction). Also, reading of Meric et al seems to teach away from Appellants' claim that there is a direct correlation between increased mRNA levels and the level of expression of the encoded protein. For example, the reference discloses that variations in mRNA sequences increase or decrease translational efficiency as found in BRCA1 (see pages 973-974). In addition, comparisons of message and protein using proteomics, show a lack of correlation, as is evidenced by Haynes et al, Gygi et al, Chen et al, Hanish S., Hanish et al, Winstead E. R. and Irving et al.

At page 25 of the response, in response to the cited art of Meric et al, Applicant reiterates that Meric supports applicants assertion that regulation of mRNA levels is the predominant mechanism of control for the majority of genes because "[t]he fundamental principle of molecular therapeutics in cancer is to exploit the differences in gene

expression between cancer cells and normal cells." Meric et al at 971. Applicant asserts that if there were no correlation between differences in mRNA and differences in protein, there would be no reason to study change in mRNA. This has been fully considered but is not found persuasive for the following reasons. It is reiterated that the focus of efforts to exploit differences in gene expression at the level of mRNA between cancer cells and normal cells coincided with the advent of cDNA array technology, which facilitated this type of approach (Meric et al, p. 971, left column first paragraph of introduction), rather than some art accepted "general correlation" between differences in mRNA and protein. Applicant also asserts that at any point in the process of producing a polypeptide involved in cancer may be exploited as a target for therapy and the inclusion of the translational machinery amongst the many potential target points does not indicate in any way that there is no correlation between mRNA and polypeptide levels. This has been fully considered but is not found persuasive for the following reasons. While targeting the translation machinery does not necessarily imply that there is a correlation between mRNA and protein levels, it also does not necessarily imply that there is a correlation. The fact that the translational machinery is being targeted in the art evinces that those skilled in the art recognize that gene expression is regulated at numerous levels and tracking the chemical intermediate mRNA, or middle step involved in translating DNA into protein reveals nothing about protein function, the abundance of protein in a cell, and modifications to proteins after they are produced – changes that may be critical in the development of diseases. It should be noted that Applicants have "acknowledged that gene expression is regulated at numerous levels."

(pg. 22, lines 3-4 of the response). Furthermore, there is insufficient information or experimental data presented on whether the PRO180 polypeptides of the present invention can serve as a reliable diagnostic marker for lung and rectal tumors. Moreover, the specification does not establish a causative link between the polypeptide of the present invention and lung or rectal tumors. Without such critical information, one skilled in the art would not be able to use the polypeptide of the present invention as a therapeutic target for treatment of lung and rectal tumors without further experimentation. The information disclosed in the instant specification is preliminary at best as there is no evidence or data that a change in PRO180 mRNA or polypeptide expression is tumor-dependent, consistent and measurable. Finally, the art indicates that the changes in mRNA expression do not correlate with polypeptide levels (e.g., Hu et al, Haynes et al, Gygi et al, Chen et al, Hanash S., Hanash et al, Winstead E. R. and Irving et al, *discussed supra*). Clearly further research would be required to reasonably confirm the real world context of the asserted utility, i.e., whether the PRO180 polypeptide can serve as a reliable diagnostic marker for lung and rectal tumors or as a therapeutic target for treatment of lung and rectal tumors. Accordingly, the claimed utility is not substantial.

At page 28 of the response, Applicant argues that the asserted utility for PRO180 as a cancer diagnostic is specific. The examiner agrees. It is reiterated that the asserted utilities are credible and specific, however, they are not substantial for the reasons of record and reiterated above.

Therefore, considering the evidence as a whole it is believed that the rejection should be sustained.

11. The rejection of claims 42-45, 47 and 49-55 under 35 U.S.C. 112, first paragraph, is maintained. Applicant submits that the discussion above under 35 U.S.C. 101 establishes a substantial, specific and credible utility for the claimed invention. In view of the discussion above, the claimed invention is not supported by a substantial utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

12. The rejection of claims 42-43 and 52-55 under 35 U.S.C 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention is maintained.

The response filed 12/9/2005 has been carefully considered, but is deemed not to be persuasive. Applicant again reviews the evidentiary standard regarding the legal presumption of written description. Again the examiner takes no issue with Applicant's discussion of the evidentiary standard regarding the legal presumption of written description. The response argues that the claims have been amended to recite that the claimed polypeptides have at least 95% amino acid sequence identity to several polypeptides related to SEQ ID NO:2 (and not SEQ ID NO:180) and satisfy the limitation

"wherein said isolated polypeptide is more highly expressed in rectal tumors or normal lung compared to normal rectum or lung tumors respectively, or wherein said isolated polypeptide is encoded by a polynucleotide that is more highly expressed in rectal tumors or normal lung compared to normal rectum or lung tumors respectively" or "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:2 in rectal or lung tissue samples." Applicant maintains that there is no substantial variation within the species, which fall within the scope of the amended claims. Applicant argues that the instant claims are analogous to the claims discussed in Example 14 of the written description training materials, in which written description was found to be satisfied for claims relating to polypeptides having 95% homology to a particular sequence and possessing a particular activity, even though applicant had not made any variants. This has been fully considered but is not found persuasive for reasons already of record. Again, unlike example 14, which encompasses a genus of molecules having significant structural similarity and defined biological functions, the genus of polypeptides of the present claims may have functions and structures that differ greatly from that of PRO180, therefore, one of skill in the art would not be able to identify the encompassed molecules as being identical to those instantly claimed. Further, the specification does not disclose any polypeptides that are 95% or 99% identical to SEQ ID NO:2 and is more highly expressed in rectal tumors or normal lung compared to normal rectum or lung tumors. Also, unlike Example 14 of the written description training materials, the polypeptide of SEQ ID NO:2 is not disclosed as having any

particular function or biological activity. Conception does not occur unless one has a mental picture of the structure of the molecule, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it.

Additionally, the claims encompass polypeptides where the only distinguishing characteristic is partial structural identity with SEQ ID NO:2, such as 95% or 99% amino acid sequence identity with amino acids 34-53, 114-121 or 181-266 of SEQ ID NO:2. Thus, the claims are drawn to polypeptides having at least 95% amino acid identity with only 7 amino acids (i.e., 114-121) out of the entire 266 amino acids of SEQ ID NO:2. Clearly, and contrary to applicants assertion there is substantial variation within the species which fall within the genus. There is no functional limitation with respect to these partial structures of SEQ ID NO:2 and as above, the encompassed polypeptides may have substantially different structures and biological functions. This is not similar to example 14 of the written description training materials, which is drawn to polypeptides having 95% homology to a particular sequence and possessing a particular catalytic activity, which uniquely distinguishes members of the genus by structure and function. The only distinguishing characteristic of the present claims is sequence identity or partial sequence identity in the case of the "extracellular domain".

The response argues with the case law of *In re Wallach* stating that the facts are similar to the instant case. Applicant's arguments have been fully considered but is not found persuasive. The facts in *In re Wallach* indicate that possession of a complete amino acid sequence of a particular protein may put the inventor in possession of a

genus of DNA sequences encoding it. The instant case differs in that the present claims are drawn to a genus of polypeptides and not a genus of DNA sequences encoding a particular protein sequence. While the skilled artisan could readily envisage the genus of DNA sequences that encode a particular protein for which the amino acid sequence has been disclosed, the skilled artisan cannot readily envisage the genus of polypeptides of the claimed invention, which may have substantially different structures and functions. Further, the present claims are directed to a genus of polypeptide sequences other than SEQ ID NO:2, e.g., at least 95% identical to amino acids 34-53, 114-121 or 181-266 of SEQ ID NO:2. Thus, there is insufficient written description for the claimed genus of polypeptides whose structures and functions may differ greatly from that of SEQ ID NO:2. Again, the specification does not disclose the biological function or activity of PRO180 (SEQ ID NO:2).

13. The rejection of claims 42-43 and 50-55 under 35 U.S.C. 112, first paragraph, because the claims contain subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained.

The response filed 12/9/05 has been carefully considered, but is deemed not to be persuasive. With respect to the protein variants encompassed by the claims, applicant states that there is not substantial variation within the claimed species of polypeptides. In response to applicants argument, it is reiterated that the claims are drawn to amino acid sequences having at least 95% identity with SEQ ID NO:2 or parts

of SEQ ID NO:50 (i.e., amino acids 34-53, 114-121 or 181-266 of SEQ ID NO:2), which broadly encompass polypeptides that are significantly less than 95% identical to SEQ ID NO:2. Again, applicant has not provided sufficient guidance and direction to assist to enable one of ordinary skill in the art to make and use the claimed protein variants that are 95% or 99% identical to SEQ ID NO:2 much less variants that are 95% or 99% identical to only amino acids 34-53, 114-121 or 181-266 of SEQ ID NO:2 in manner reasonable correlated with the scope of the claims broadly including any number of additions, deletions, or substitutions and fragments. The specification does not teach a biological function of the claimed polypeptides and one of skill in the art would not know how to use the claimed polypeptides or screen for the same. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the changes which can be made in the protein's structure and still maintain biological activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F,2d 1200, 18 USPQ 1016 (Fed. Cir. 1991) at 18 USPQ 1026 1027 and Ex parte Forman, 230 USPQ 546 (BPAI 1986).

Due to the large quantity of experimentation necessary to generate the indefinite number of protein variants recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art (Burgess

et al, Lazar et al, Schwartz et al, Lin et al and Li et al, previously cited in the Office Action mailed 9/4/2003) which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any functional limitations, undue experimentation would be required of the skilled artisan to make and use the claimed invention in its full scope.

14. The rejection of claims 42-43 and 50-55 under 35 U.S.C. 112, first paragraph, NEW MATTER, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed is maintained in part (see item no. 9 above).

The response filed 12/9/05 has been carefully considered, but is deemed not to be persuasive. The response states that for reasons provided in the above discussion regarding the written description requirement, Applicants maintain that the specification adequately describes the claimed polypeptides. As discussed above regarding written description, the specification does not disclose or contemplate any polypeptide that is 95% or 99% identical to the polypeptide of SEQ ID NO:2 or amino acids 34-53, 114-121 or 181-266 of SEQ ID NO:2 and is more highly expressed in normal kidney or rectal tumor compared to lung tumor or normal rectum. The specification only discloses PRO180 (SEQ ID NO:2) mRNA as being more highly expressed in normal kidney or rectal tumor compared to lung tumor or normal rectum. Thus, there is insufficient written support for the claimed genus of variant PRO180 polypeptides that are more

highly expressed in normal kidney or rectal tumor compared to lung tumor or normal rectum as encompassed by the claims.

Priority

Applicant claims priority to five previous applications in the preliminary amendment of 09 September 2002. Priority is granted to PCT/US00/23328, filed 24 August 2000, as the disclosure of '328 is identical to the instant disclosure. However, priority is not granted to USSN 09/380,137, PCT/US99/12252 and 60/088,740 since these applications do not disclose the quantitative PCR analysis of a cDNA library to measure mRNA expression (i.e., Example 18) upon which applicant relies for utility of the instantly claimed polypeptides. Therefore, the filing date for the purpose of art rejections is deemed to be 24 August 2000. Applicant is reminded that benefit to a prior-filed application requires written description and enablement under the first paragraph of 35 U.S.C. 112.

15. The rejection of claims 42-45, 47 and 49-55 are rejected under 35 U.S.C. 102(b) as being anticipated by Feng et al (WO 99/24836, 5/1999) is maintained.

The response filed 12/9/2005 argues as previously with the Stempel Doctrine. Applicant states that they were in possession of so much of the claimed invention as is disclosed in WO 99/24836 prior to the publication date of WO 99/24836. Applicant also maintains that the previously submitted Declaration under 37 CFR 1.131 by Goddard et al on 12/13/2004 establishes prior invention of the claimed subject matter prior to the

Feng reference. This has been fully considered but is not found persuasive. With respect to the Stempel Doctrine, as discussed above (see "*Priority*" above), the filing date for the purpose of art rejections is deemed to be 24 August 2000 because prior applications PCT/US00/08439, USSN 09/380,137, PCT/US99/12252 and 60/096,102 do not disclose the quantitative PCR analysis of a cDNA library measuring mRNA expression. Applicant is reminded that benefit to a prior-filed application also requires written description and enablement under the first paragraph of 35 U.S.C. 112. The priority documents do not provide adequate written support for the quantitative PCR analysis of a cDNA library measuring mRNA expression (i.e., Example 18). For these reasons, the Declaration of Goddard et al filed on 12/9/2004 under 37 CFR 1.131 has been considered but is ineffective to overcome the Feng et al reference.

16. The rejection of claims 42-45, 47 and 49-55 are rejected under 35 U.S.C. 102(a) as being anticipated by Baker et al (WO 99/63088, 12/1999) is maintained.

The response maintains that the previously submitted Declaration under 37 CFR 1.131 by Goddard et al on 1/28/2004 establishes prior invention of the claimed subject matter prior to December 1999. Based on the supplied evidence, Applicant concludes that Walker et al is not available as prior art. The Declaration of Goddard et al filed on 12/13/2004 under 37 CFR 1.131 has been considered but is ineffective to overcome the Baker et al reference. As discussed above (see "*Priority*" above) the filing date for the purpose of art rejections is deemed to be 24 August 2000 because prior applications PCT/US00/08439, USSN 09/380,137, PCT/US99/12252 and 60/096,102 do not

disclose the quantitative PCR analysis of a cDNA library measuring mRNA expression. Applicant is reminded that benefit to a prior-filed application also requires written description and enablement under the first paragraph of 35 U.S.C. 112.

New Grounds of rejections

17. Claim 47 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 47 is indefinite for reciting "the extracellular domain". There is insufficient antecedent basis for this limitation. Base claim 44 recites three extracellular domains and it is unclear which "extracellular domain" is being referenced. MPEP 2173.05(e).

Conclusions

18. No claim is allowed.

19. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827

SHEELA HUFF
PRIMARY EXAMINER